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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/656,715	09/05/2003	Yang-Dar Yuan	600-69-CIP	8271

7590 11/04/2005

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EXAMINER	
LEWIS, AMY A	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 11/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/656,715	YUAN ET AL.	
	Examiner	Art Unit	
	Amy A. Lewis	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/12/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Case

Claims 1-34, as filed 5 September 2003, are presented for examination.

Priority

Status as a CIP of parent application US Serial No. 10/389,071, which is a continuation-in-part of 10/100,638 (now US Patent No. 6,740,676), filed 19 March 2002, is acknowledged.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

1) Claims 1-34 are *provisionally* rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 33-44, 46-77, and 79-89 of copending Application No. US 2003/0207931 (Vasudevan et al.), also Application Serial No. 10/389071. The compound and method of treatment of co-pending '071 claims 33-44, 46-77, and 79-89 are the same as the compounds administered in the instant application; both

applications teach a compound of the same generic formula and the corresponding pharmaceutical composition for co-administration to a mammal (including a human) which has inhibitory effects on the CP450RAI enzyme. Therefore, instant claims 1-34 are an obvious variation of the co-pending Vasudevan et al. '071 claims 33-44, 46-77, and 79-89.

This is a provisional obviousness-type double patenting rejection.

2) Claims 28-34 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-32 of US Pat. 6,740,676.

Instant claims 28-34 are directed to the same compounds and pharmaceutical compositions as claims 1-32 of US Pat. 6,740,676, and are thus an obvious variation.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting the enzyme P450RA with the claimed compounds *in vitro*, and for a method of treating the skin disorder plaque psoriasis in a mammal by administering the CP450RAI inhibitor liarozole or retinoic acid, does not reasonably provide enablement for preventing or treating *any* condition treatable by a retinoid or controlled by the mammal's native retinoic acid with the claimed compounds co-adminisered with a retinoid or a compound having vitamin a activity. The specification does not enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) Nature of the invention.
2) State of the prior art.
3) Relative skill of those in the art.
4) Level of predictability in the art.
5) Amount of direction or guidance provided by the inventor.
6) Presence or absence of working examples.
7) Breadth of the claims.
8) Quantity of experimentation necessary to make or use the invention based on the content of the disclosure.

The instant specification fails to provide guidance that would allow the skilled artisan to practice the instant invention without resorting to undue experimentation, as discussed in the subsections set forth hereinbelow. While all of these factors are considered, a sufficient number are discussed below so as to create a *prima facie* case.

The claims are extremely broad and drawn to a method of treating *any* disease related to retinoic acid or the mammal's native retinoic acid by co-administering the claimed compound and/or a retinoid (see p. 7-8 of the specification, which cites a variety of conditions). The enablement for treatment of the skin disorder plaque psoriasis with liarozole (a known inhibitor of CP450RA) is based solely upon the prior art: Kuijpers A. et al. "The effects of oral liarozole on epidermal proliferation and differentiaion in severe plaque psoriasis are comparable with

those of acitretin," 1998 *British J of Dermatology* 139: 380-389, cited by Applicant on page 6 of the specification. It is also known to treat several skin diseases, including acute promyelotic leukaemia, psoriasis, seborrhea, severe acne, rosacea, and acneform dermatoses with the retinoids tretinoin, etretinate and acitretin (See Orfanos CE et al. "Current use and future protential role of retinoids in dermatology," March 1997 *Drugs* 53(3): 358-388). It is also noted that while Orfanos teaches various specific retinoid compounds, it does not teach inhibitors of CP450RA. The guidance provided by the specification regarding treatment of psoriasis (or any other diseases, including those of the skin) are not *per se* described or enabled by the specification; enablement is solely based upon the prior art.

Regarding the amount of direction or guidance provided by the inventor and the presence or absence of working examples (factors 5 & 6), the specification merely provides a test of skin irritation and a P450RA inhibition assay. Table 1 demonstrates the ability of the claimed compounds to inhibit P450RA *in vitro* (see p. 11-16 of the specification). The specification merely provides a test of topical skin irritation for disclosed compounds where Z is COO, and those where Z is c[triple bond]C were not tested in this assay (Table 3, pages 15-18). The specification lists a breadth of diseases and provides while providing no guidance regarding dosages or treatment regimens for any disease related to retinoic acid or the mammal's native retinoic acid with the claimed compounds.

The specification does not enable any person skilled in the art to which it pertains (i.e. treatment of retinoic acid related diseases) to make or use the invention commensurate in scope with the claims. Applicants fail to provide the guidance and information required to ascertain

which particular type of retinoic acid related disease the claimed compounds agent will be effective against without resorting to undue experimentation.

In addition, the burden of enabling the prevention of a retinoic acid related condition such as psoriasis for example, would be much greater than that of enabling the treatment of the condition. In the instant case, the specification does not provide guidance as to how one skilled in the art would accomplish the objective of preventing conditions related to retinoic acid or how a patient could be kept from every being susceptible to this condition. Nor is there any guidance provided as to a specific protocol to be utilized in order to show the efficacy of the presently claimed active agents for preventing such conditions.

The term "prevention" is synonymous with the term "curing" and both circumscribe methods of absolute success. Since absolute success is not reasonably possible with most diseases/conditions, especially those having etiologies and pathophysiological manifestations as complex as retinoic acid related disorders (for example psoriasis), the specification, which lacks an objective showing that cystic fibrosis can actually be prevented, is viewed as lacking an adequate written description of the same.

Absent a reasonable *a priori* expectation of success for using the claimed compounds to treat any particular type of retinoic acid related disorder, one skilled in the art would have to extensively test many various diseases with the claimed compounds. Since each prospective embodiment, and indeed future embodiments as the art progresses, would have to be empirically tested, and those which initially failed tested further, an undue amount of experimentation would

be required to practice the invention as its is claimed in its current scope, because the specification provides inadequate guidance to do otherwise.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1) Claims 1-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The terms "a retinoid" and "a derivative of vitamin A having vitamin A like biological activity" in claims 1 and 28 are not defined by the claim, and the specification does not provide a definition for what is meant by these terms. It is noted that the specification states "compounds that have retinoid-like activity are well known in the art," but does not explicitly define what is meant by a "retinoid" or what is meant by vitamin A like biological activity. Thus, one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

"The primary purpose of this requirement of definiteness of claim language is to ensure that the scope of the claims is clear so the public is informed of the boundaries of what constitutes infringement of the patent. A secondary purpose is to provide a clear measure of what applicants regard as the invention so that it can be determined whether the claimed invention meets all the criteria for patentability and whether the specification meets the criteria of 35 U.S.C. 112, first paragraph with respect to the claimed invention" (MPEP 2173)

Because the terms "a retinoid" and "a derivative of vitamin A having vitamin A like biological activity" would invite subjective interpretations of whether or not a particular compounds or instance of administration was included by or excluded from the present claims, it is the Examiner's position that the public would not be informed of the boundaries of what

constitutes infringement of the present claims, and thus the claims do not meet the requirements of 35 U.S.C. § 112, second paragraph. In other words, the specification does not specifically define what is meant by "a retinoid," a "derivative of vitamin A," or what is meant by "vitamin A like biological acivity."

2) Claims 17-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The structures recited in claims 17-23 have a hydrogen in the R_2 location. However, in claim 16, R_2 recites several specific moieties, but hydrogen is ***not*** listed among the specified moieties. Therefore, there is insufficient antecedent basis for this limitation in these claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-9 and 28-32 are rejected under 35 U.S.C. 102(b) as being anticipate by Granger et al. US Patent Application No. US 2004/0043044 A1.

Granger et al. teaches that natural and synthetic vitamin A (retinol) compounds have been used extensively to "treat a variety of skin disorders, e.g., acne, wrinkles, proriasis, age spots, and discoloration." The reference also teaches that certain compounds, termed "boosters," when used alone or in combination with each other, potentiate the action of retinoids by increasing the

conversion of the retinoids to retinoic acid. One of the "boosters" cited by Granger are inhibitors of cytochrome P450 dependent retinoic acid oxidation ([0006]). The reference teaches compositions with include a retinoid (e.g. retinol, retinyl esters, retinal, retinoic acid) co-present with a booster or combination of boosters to optimize efficacy of the composition. (See p. 1 [0001-0007, 0115]).

Conclusion

Claims 1-34 are rejected. No claims are allowed.

Contact Information:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy A. Lewis whose telephone number is (571) 272-2765. The examiner can normally be reached on Monday-Friday, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571) 272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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